EXPERIMENTAL STUDIES ON CARBOHYDRATE METABOLISM DURING HEART LUNG BYPASS, WITH SPECIAL REFERENCE TO A COMPARISON OF PULSATILE FLOW WITH NON-PULSATILE FLOW

by

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INTRODUCTION

Since the day that the heart lung machine was first used clinically surgical procedures on the heart have made remarkable progress It cannot be said however, that all problems in connection with heart lung bypass are completely solved, For example, many unpleasant phenomena such as low arterial pressure, metabolic acidosis and others are often observed during prolonged heart lung bypass, even with relatively high flow rates.[5)3)14)15)16)] The causes of these unpleasant phenomena have not yet been clarified. The change in the dynamics of blood flow, namely the diminution or disappearance of pulsation which is often observed during total bypass seems to be one of the important causative factors, and the question whether pulsatile flow or non-pulsatile flow should be used for heart lung bypass is still a subject of discussion.

The present investigation, therefore, was undertaken to clarify the above problem. Careful investigations were made on carbohydrate metabolism during total heart lung bypass, at normothermia and mild hypothermia, using pulsatile and non-pulsatile blood flows.

EXPERIMENTAL STUDIES

1. Changes in the Carbohydrate Metabolism of the Blood during Heart Lung Bypass at Normothermia

A. Experimental Methods and Materials

Fifty healthy adult mongrel dogs, weighing 8 to 12 kilograms were anesthetized with intravenous pentobarbital sodium (25 to 30 milligrams per kilogram of body weight). Respiration was maintained with intermittent positive pressure with pure oxygen. For the determination of lactic acid metabolism in the liver during heart lung bypass, a Cournand catheter was inserted through the right jugular vein into the hepatic vein under X-ray control At the same time, a small vinyl tube was inserted into the portal vein through the small abdominal incision. After these procedures, the chest was opened by an incisions through the right fourth and the left third intercostal spaces. The azygos vein was ligated and sling ligatures were placed around both vena cavae. Three milligrams of heparin per kilogram of body weight were given intravenously after all dissections had been completed. For arterial blood delivery a metal cannula of 3 mm. in diameter was inserted through the left carotid artery into the aorta, and for venous cannulation two vinyl tubes of 5-6 mm in diameter were passed through the right atrium into both vena cavae. Venous blood was drained by gravity at a negative pressure of about 50 cm H_2O and collected in the reservoir.

The artificial heat employed was a new type of pulsatile pump nconstructed in our laboratory under the direction of Dr. GORO KAMIMOTO, Professor of the Faculty of Technology, Kyoto University[18)19)].

For oxygenation of the venous blood, a WAUD-SALISBURY type oxygenator was used[22)29)].

The flow rate during heart lung bypass was accurately determined with an electromagnetic flowmeter or a rotameter. The arterial pressure was recorded from the femoral artery, and the venous pressure from the inferior vena cava.

Throughout the experiment the pulse rate was set at 70 to 80 per minute, and when non-pulsatile flow was used, pulsation was removed by an air chamber interposed in the delivery tube.

The animals were divided into two groups. Observations were made on each group with either pulsatile or non-pulsatile flow with the flow rate varying from 50 to 120 cc/kg/min. for a period of sixty to ninety minutes of heart lung bypass. Care was taken to keep the rectal temperature above 36°C during the procedure. Samples of venous blood were taken from the right atrium immediately after opening the chest.

After starting heart lung bypass samples of blood were taken from the venous line of the heart lung machine. Lactic acid was determined according to the method of BARKER and SUMMERSON[3)], pyruvic acid by the method of FRIEDMANN and HAUGEN[7)] and blood sugar was determined as described by SOMOGYI[15)]. The blood proteins were precipitated in chilled trichloracetic acid within thirty seconds after drawing the sample.

B. Results (Tables 1 and 2)

Fig. 1: Changes of lactic acid in the blood during total heart lung bypass at normothermia, using puls atile and non-pulsatile blood flows.

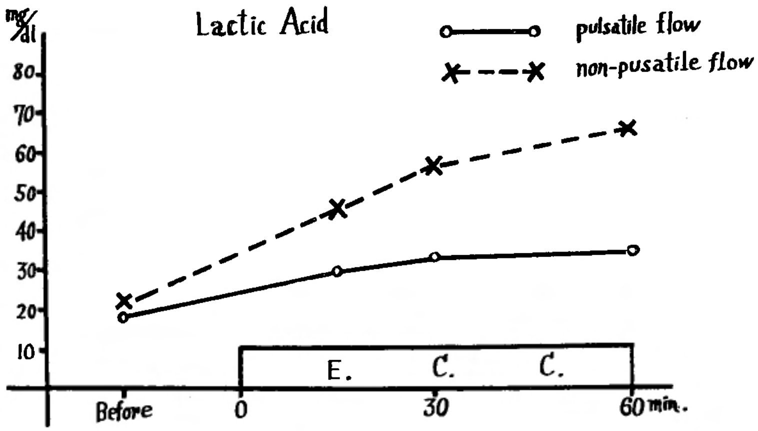


Table 1 Pulsatile flow group (normothermia)

No.	Flow Rate	Time	Blood Sugar	Lactic Acid			Pyruvic Acid	L/P Ratio	Ext. Rate
				Mixed Venous Blood	Portal Vein	Hepatic Vein			
	cc/kg/min.	min.	mg/dl	mg/dl	mg/dl	mg/dl	mg/dl		%
17	90	Pre.							
		15		37.8					
		30		33.0					
		60		39.0					
21	70	Pre.		3.8					
		15		20.2					
		30		29.6					
		60		40.5					
33	100	Pre.		25.0	30.0	20.7	2.20	11.3	31.0
		15		38.0	34.3	30.2	1.82	20.9	11.9
		30		38.7	42.0	30.9	3.43	11.2	26.4
		60		41.1	55.6	47.1	3.47	11.8	15.2
35	90	Pre.		27.1			2.49	10.8	
		15		30.4			3.31	9.1	
		30		31.4			3.56	8.8	
		60		28.9			4.40	6.5	
36	100	Pre.	89.5						
		15	95.0						
		30	108.0						
		60	118.0						
41	50	Pre.	71.6	13.5	13.0	8.6	1.12	12.0	33.8
		15	92.0	20.5	19.5	17.0	2.22	9.2	12.8
		30	110.0	33.5	30.5	20.2	2.35	14.2	33.7
42	50	Pre.	94.0	14.5	11.2	2.3	1.97	7.3	79.4
		15	115.0	23.7	21.1	18.2	2.85	8.3	13.7
		30	121.0	31.0	29.0	23.5	3.40	9.1	18.9
		60	117.0	33.0	29.2	17.8	3.52	9.3	39.0
47	65	Pre.	102.0	25.8			2.53	10.1	
		15	126.0	30.7			2.92	10.5	
		30	138.0	42.3			2.98	14.1	
		60	164.0	41.7			2.93	14.2	
49	100	Pre.	116.5	12.5	12.3	7.5	1.63	7.6	39.0
		15	106.0	25.0	24.3	19.0	2.66	9.3	21.8
		30	119.0	22.7	29.7	21.5	2.29	9.9	27.6
		60	127.0	34.8	36.7	33.5	2.18	15.9	8.7
62	80	Pre.		24.3			2.77	8.7	
		15		33.8			3.78	8.9	
		30		34.1			4.09	8.3	
		60		46.0			3.92	11.7	
Average		Pre.	94.7	18.3			2.10	9.6	45.8
		15	106.8	28.9			2.79	10.8	15.0
		30	119.2	32.9			3.15	10.8	26.6
		60	131.9	33.9			3.40	11.8	20.9

Notes : Pre. ; Before the total heart lung bypass.
Ext. Rate ; Extraction rate of lactic acid by the liver.

Table 2 Non-pulsatile flow group (normothermia)

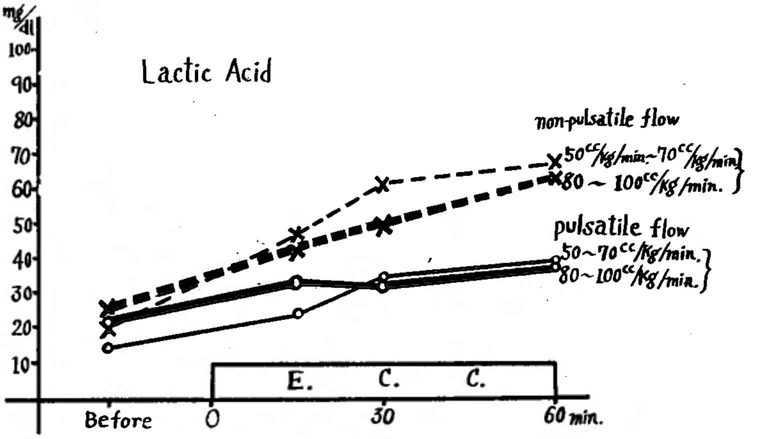
No.	Flow Rate	Time	Blood Sugar	Lactic acid Mixed Venous Blood	Lactic acid Portal Vein	Lactic acid Hepatic Vein	Pyruvic Acid	L/P Ratio	Ext. Rate
	cc/kg/min.	min.	mg/dl	mg/dl	mg/dl	mg/dl	mg/dl		%
18	50	Pre. 15 30 60		22.8 42.1 66.7 58.0					
22	60	Pre. 15 30 60		17.5 47.0 61.0 79.1					
25	70	Pre. 15 30 60	167.0 163.0 204.0 225.0	24.1 55.8 108.0 117.0					
29	100	Pre. 15 30 60	 120.0 159.0 143.0	 55.0 61.0 64.0			 2.93 3.13 3.21	 18.7 19.4 19.9	
37	70	Pre. 15 30 60	88.5 84.0 104.5 141.5	20.5 44.8 43.8 46.8					
38	90	Pre. 15 30 60	95.3 115.0 139.0 151.0	31.0 48.5 52.9 72.0	35.1 39.2 48.8 65.8	24.9 40.0 46.5 63.4	2.77 3.24 3.32 3.46	11.1 14.9 15.9 20.8	29.0 −2.0 4.7 3.6
39	80	Pre. 15 30 60	79.5 122.5 142.8 183.8	25.5 34.3 49.8 61.2	30.0 41.3 52.7 72.0	18.8 24.6 45.6 47.5	2.22 2.88 3.53 4.08	11.4 11.9 14.1 15.0	37.3 40.4 15.3 34.0
40	70	Pre. 15 30 60	77.0 78.5 97.6 116.0	21.0 31.0 41.3 42.2	19.5 33.0 42.2 44.8	5.8 26.8 38.2 39.1	2.19 2.79 4.32 4.25	9.5 11.1 9.5 9.9	73.3 18.7 9.4 12.7
48	95	Pre. 15 30 60	113.0 141.0 146.0 152.5	21.0 34.0 34.8 55.8	16.2 38.8 36.5 39.0	9.5 31.2 33.0 30.0	2.16 3.47 3.86 4.08	9.7 9.7 9.0 13.7	41.3 19.5 9.5 23.0
50	60	Pre. 15 30 60	77.5 93.5 96.0 110.0	17.5 62.5 47.7 59.0	7.5 54.0 64.5 64.2	4.5 56.1 44.6 63.0	1.68 2.17 2.31 3.08	10.4 28.8 20.6 19.1	40.0 −3.8 30.8 1.8
Average		Pre. 15 30 60	99.6 127.1 136.1 152.8	22.3 45.5 56.7 65.5			2.20 2.91 3.41 3.69	10.4 15.8 14.7 16.4	44.1 14.5 13.7 15.0

(1) Lactic acid of the blood

In the pulsatile flow group no significant increase in lactic acid was measurable even thirty minutes after the commencement of total bypass. On the other hand, in the non-pulsatile flow group, an obvious increase of blood lactic acid was noted 15 minutes after the start of total bypass. The difference between the two groups became more pronounced after one hour of perfusion (Fig. 1).

Defining 80 cc/kg/min. or more as a high flow rate, and less than 80 cc/kg/min. as a low flow rate, the increase of lactic acid in the blood was much less in the high flow group than in the low flow rate group after total bypass of 60 minutes. Furthermore, within the low flow rate group, there was a definite difference noticeable between the pulsatile and non-pulsatile group already after 15 minutes of perfusion. This difference also appeared gradually within the high flow rate group. It usually was not marked after a perfusion of 15-30 minutes, but became prominent gradually after a perfusion of 60 minutes and more (Fig. 2).

Fig. 2 : Changes of lactic acid in the blood during total heart lung bypass at normothermia, using pulsatile and non-pulsatile blood flow, dividing the blood flow rate in two groups ; 80 cc/kg/min. or more as a high flow rate, and less than 80 cc/kg/min. as a low flow rate.



As for the relationship of the rate of lactic acid production and the blood pressure, the increase of lactic acid in the blood was not significant when the blood pressure was maintained satisfactorily.

On the other hand, when the blood pressure fell below 80 mm Hg., the increase of lactic acid in the blood usually was considerable (Figs. 3 and 4).

In connection with the early increase of lactic acid in the blood which was observed in both groups, the amount of lactic acid accumulated in the priming blood before commencement of heart lung bypass should be considered. The lactic acid level of the priming blood averaged 35 mg/dl. This is the result of an anaerobic glycolysis which occurs during storage of blood. It is also known that the blood lactic acid level increases at the rate of 16.5 mg/dl per hour at a temperature of 37.5°C.[1]

(2) Extraction rate of lactic acid by the liver (Fig. 5)

Fig. 3 The relatioaship of the rate of lactic acid production and the blood pressure during total heart lung bypass at normothermia, using pulsatile blood flow, with a blood flow rate of 70cc/kg/min.

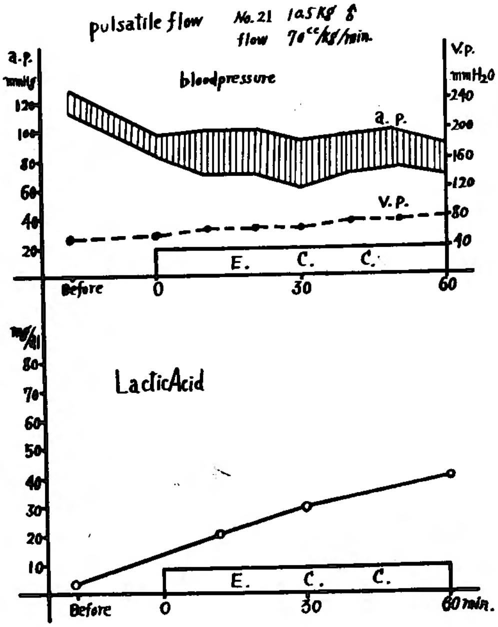


Fig. 4: The relationship of the rate of lactic acid production and the blood pressure during total heart lung bypass at normothermia, using non-pulsatile blood flow, with a blood flow rate of 70 cc/kg/min.

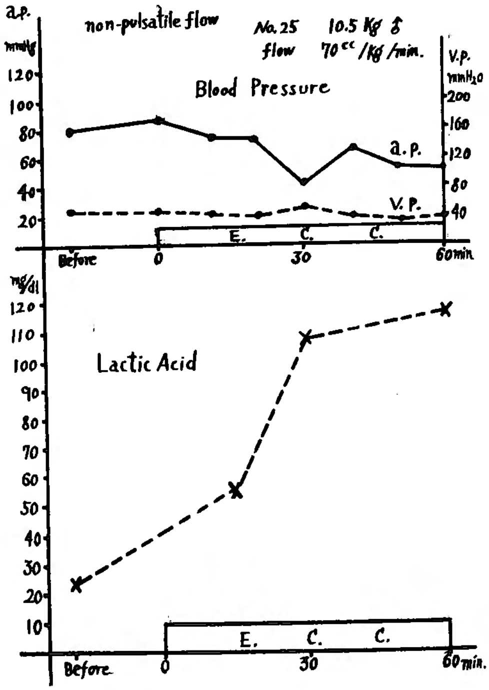
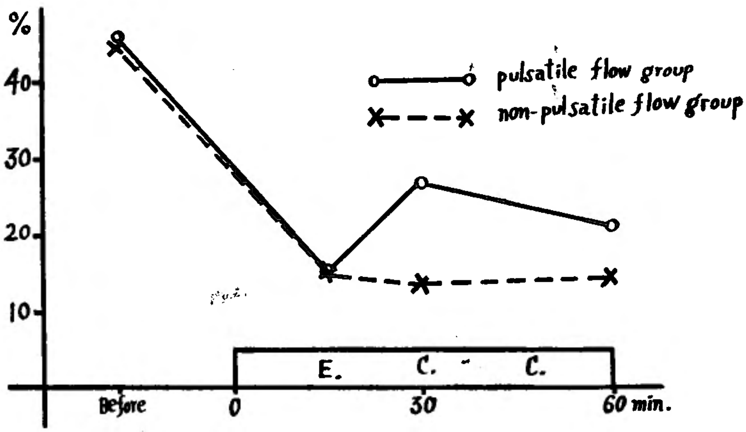


Fig. 5 : Extraction rate of lactic acid by the liver.



Taking blood samples simultaneosly from the portal vein and from the hepatic vein, the extraction rate of lactic acid by the liver was calculated according to the formula shown below.

$$\text{Extraction rate} = \frac{\text{PLA} - \text{HLA}}{\text{PLA}} \times 100$$

(In the equation, PLA = lactic acid of portal vein blood
HLA = lactic acid of hepatic vein blood)

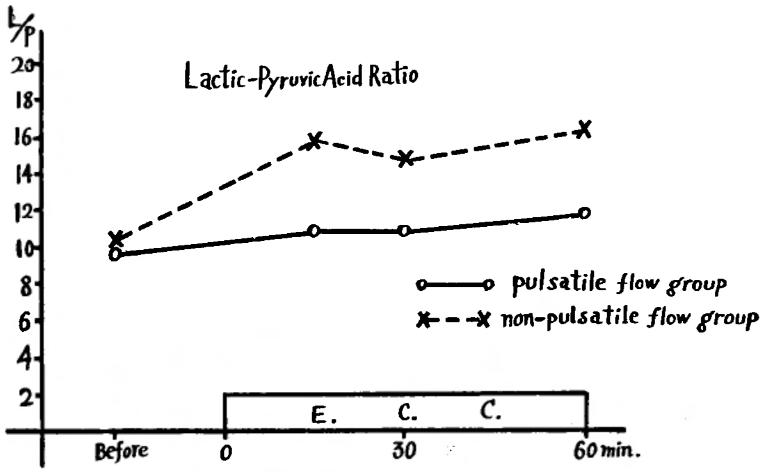
The extraction rate of lactic acid by the liver became conspicuously lower in both pulsatile and non-pulsatile flow groups after perfusion of 15 minutes. This decreased extraction rate seems to be due to the fact that the priming blood, which contained high concentrations of lactic acid, passed through the liver during the early stage of heart lung bypass. Subsequently, however, the extraction rate was greater in the pulsatile flow group than in the non-pulsatile flow group suggesting that liver function was better in the pulsatile flow group.

(3) Pyruvic acid

The difference in pyruvic acid between the two groups was not so remarkable, however it was increased in the non-pulsatile flow group.

(4) Lactic-pyruvic acid ratio (Fig. 6)

Fig. 6: Lactic-pyruvic acid ratio during extracorporeal circulation at normothermia, using pulsatile and non-pulsatile blood flow.



In the pulsatile flow group, the L/P ratio did not increase and was maintained at almost the same level as before perfusion. In the non-pulsatile flow group, however, the ratio increased to 16/1 after one hour of total perfusion. This fact indicates that the oxygen supply to the peripheral tissues was maintained much better in the pulsatile flow group.

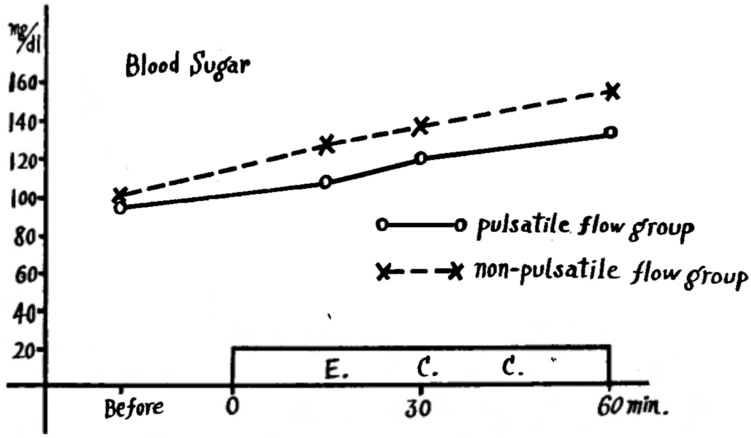
(5) Blood sugar (Fig. 7)

The difference between the two groups was less evident here than in the case of lactic acid. However, in general the non-pulsatile flow group showed an increase of blood sugar levels.

C. Discussion.

It is a well-known fact that lactic acid and blood sugar as well as pyruvic acid increase abnormally during hypoxia. According to SAMUEL SOSKIN[13] the interrelation

Fig. 7: Blood sugar during extracorporeal circulation at normthermia, using pulsatile and non-pulsatile blood flow.



between lactic acid and pyruvic acid is reversible (lactic acid ⇆ pyruvic acid), and the question as to which side this reversible reaction is inclined has to be solved by answering the question whether diphosphopyridine nucleotide (D. P. N. the coenzyme constituting the lactic acid acidification enzyme) is present in the oxidization form. Under normal condition D. P. N. is alway spresent in the oxidization form. Furthermore the deoxidization form of D. P. N. switches over to its oxidization form as soon as its hydrogen element are transferred to a hydrogen acceptor. The pyruvic acid thus produced easily enters into the tricarboxylic acid cycle (the ultimate oxidization process) and is completely dissolved by oxidization, being turned into carbon dioxide and water.

However, under conditions of any lack of oxygen the deoxidization form of D. P. N., unable to find any other hydrogen acceptor, now uses pyruvic acid as the only available hydrogen acceptor, so under anaerobic conditons pyruvic acid is reduced to lactic acid, which results in the absolute or relative increase of lactic acid and thus an increase of the lactic-dyruvic acid ratio.

This theory has been generally accepted since FRIEDMANN[8] proved the abnormal increase of the L/P ratio during hypoxia[24)11]. An increase of the L/P ratio means a greater increase of lactic acid than of pyruvic acid. So it is only natural that this L/P ratio increase can act as a sort of barometer which shows the balance between aerobic and anaerobic metabolism in the body, as RUSSEL[20], ENGEL[5] and others stated.

According to our experiments, lactic acid in the blood in the pulsatile flow group did not show a marked increase, whereas in the non-pulsatile flow group it showed an abnormal increase as soon as heart lung bypass was started. However, with higher flow rates this difference in the blood lactic acid level, although still more significantly in the non-pulsatile flow group than in the pulsatile flow group, decreased.

For example, when we carried out extracorporeal circulation with a flow of more than 80 cc/kg/min. the increase of lactic acid was extremely slight, whereas in the nonpulsatile flow group, with the same flow rate the increase was fairly great. The same holds for pyruvic acid; the increase of which was more marked in the non-pulsatile flow group.

As to the L/P ratio in the pulsatile flow group, it's increase was extremely slight, whereas in the non-pulsatile flow group it showed a great increase even within fifteen minutes after starting heart lung bypass. In short, it is rather apparent in the non-pulsatile flow group that the peripheral tissue was suffered from hypoxia during heart lung bypass. ANDERSON[2] observed almost no decrease in extraction rate of lactic acid by the liver during heart lung bypass of one hour, but he observed a marked acidosis with an abnormal increase of lactic acid in the peripheral tissue. SAEGUSA[21], who carried out heart lung bypass for relatively short period with high blood flow noted no lowering of the extraction rate of lactic acid but also no remarkable difference in the functional disorders of the liver after perfusion. In our experiment the extraction rate showed a marked decrease in both geoups as soon as heart lung bypass was started, and this is seemed to be a result of high concentration of lactic acid which was already present in the priming blood as described above. However, no decrease in the extraction rate was observed after that; moreover, the extraction rate showed a tendency to increase in the pulsatile flow group.

TAKEDA[28], one of our co-workers, observed microscopically the behavior of the capillary vessel of the omentum during heart lung bypass. He noticed that in the non-pulsatile flow group the blood stream of the true capillaries became gradually slower and finally stopped completely and the blood passed mainly through the preferential channels or the A-V anastomoses, which caused edema in the tissues and even a tissue hypoxia. NONOYAMA[17] also pointed out that in the non-pulsatile flow group the oxygen consumption of the body became abnormally small and the peripheral tissue might be hypoxic. These observations correspond well with my findings that the blood lactic acid level and the L/P ratio increased abnormally in the non-pulsatile flow group showing the presence of tissue hypoxia during heart lung bypass.

II. Changes in the Carbohydrate Metabolism of the Blood during Heart Lung Bypass in Conjunction with Mild Hypothermia

Recently the combination of hypothermia and pump oxygenator has been markedly improved and many good results have been reported.

The combination of these two methods permits the use of a lower blood flow, which offers a number of possible advantages including simplicity of cannulation and of the pump oxygenator design and reduction of blood trauma.

In this experiment, carbohydrate metabolism was investigated in the pulsatile flow group and non-pulsatile flow group during heart lung bypass in conjunction with mild hypothermia (29°～30°C).

Also the difference between normothermia and hypothermia was investigated.

A. Experimental Methods and Materials

To provide for direct blood cooling and rewarming in these animal experiments, a blood heat exchanger (coil-winded vinyl tube) was put in the circuit of the heart and lung machine. By this method, the body temperature was reduced on the average of 1°C per minute. Then rectal temperature was maintained throughout heart lung bypass at 29°C～30°C.

B. Results (Tables 3 and 4, and Figs. 8, 9, 10, 11 and 12)

(1) Lactic acid

In general the blood lactic acid level in the pulsatile flow group remained low in comparison with that of the non-pulsatile flow group.

For example, with a blood flow rate of 70 cc/kg/min., the non-pulsatile flow group showed a conspicuous increase of lactic acid level in the blood, whereas the pulsatile flow group showed no increase during heart lung bypass. However, with a blood flow rate of 30cc～50cc/kg/min., almost no difference was observed between the two groups.

(2) Pyruvic acid

The difference between the two groups was not so noticeable. However, a slight tendency towards an increase was observed in the non-pulsatile flow group.

(3) Lactic-pyruvic acid ratio

In the pulsatile flow group the L/P ratio did not show a significant increase, and with relatively high blood flow such as 70 cc/kg/min., the L/P ratio was quite constant. On the other hand, the L/P ratio increased in the non-pulsatile flow group even with the identical blood flow rate of 70cc/kg/min.

Fig. 8: Changes of blood sugar, lactic acid in the blood, and L/P ratio during total heart lung bypass at mild hypothermia, using pulsatile and non-pulsatile blood flow, with a blood flow rate of 70cc/kg/min.

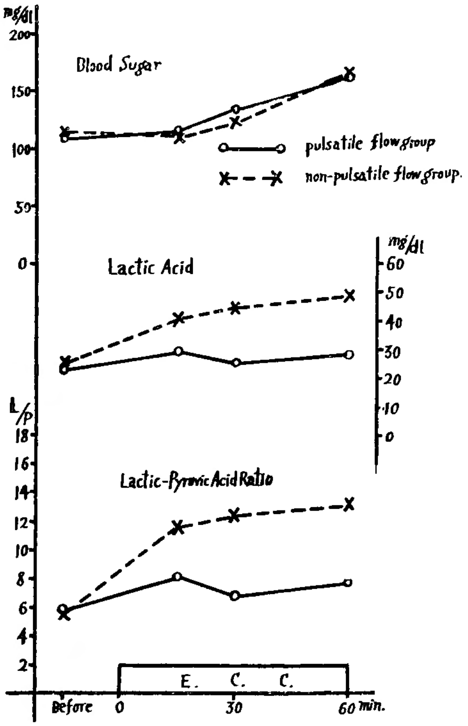
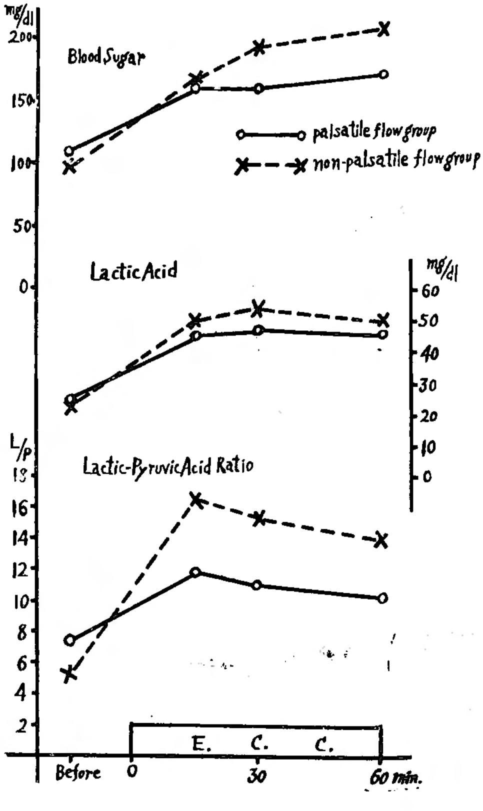


Fig. 9: Changes of blood sugar, lacti cacid in the blood, and L/P ratio during total heart lung bypass at mild hypothermia, using pulsatile and nonpulsatile blood flow, with a blood flow rate of 50cc/kg/min.



(4) Blood sugar

In general the increase of blood sugar levels in the non-pulsatile flow group is more manifest than in the pulsatile flow group. However with a blood flow rate of 70 cc/kg/min., it is hard to notice a difference between the two groups. As for the relationship of blood flow rate and blood sugar level, the lower the flow rate was employed, the more marked increase of blood sugar level was observed. This tendency, however, was not so remarkable until after 30 minutes of perfusion.

(5) Comparisons of the carbohydrate metabolism between normothermia and mild hypothermia

Fig. 13 shows the changes in carbohydrate metabolism during heart lung bypass with normothermia and mild hypothermia. As a rule, with mild hypothermia the increase of lactic acid in the blood and of the L/P ratio is less in both pulsatile and non-pulsatile flow groups than with normothermia. However, the blood sugar level is rather high in both groups during heart lung bypass under mild hypothermia.

Fig. 10: Changes of blood sugar, lactic acid in the blood, and L/P ratio during total heart lung bypass at mild hypothermia, using pulsatile and non-pulsatile blood flow, with a blood flow rate of 30cc/kg/min.

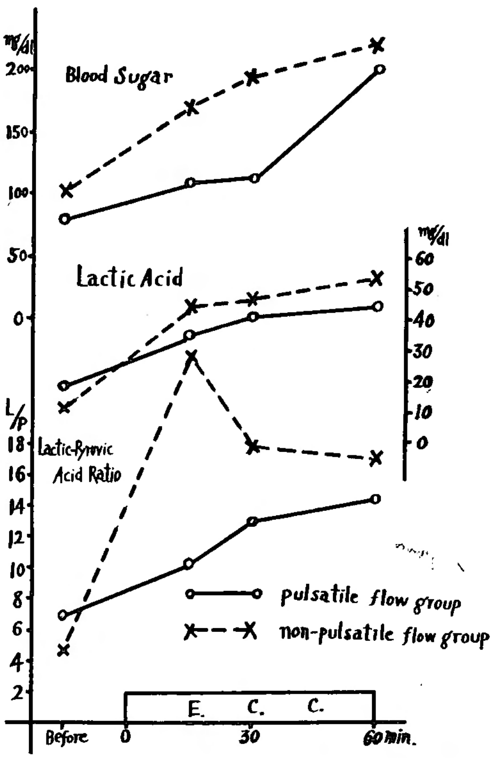
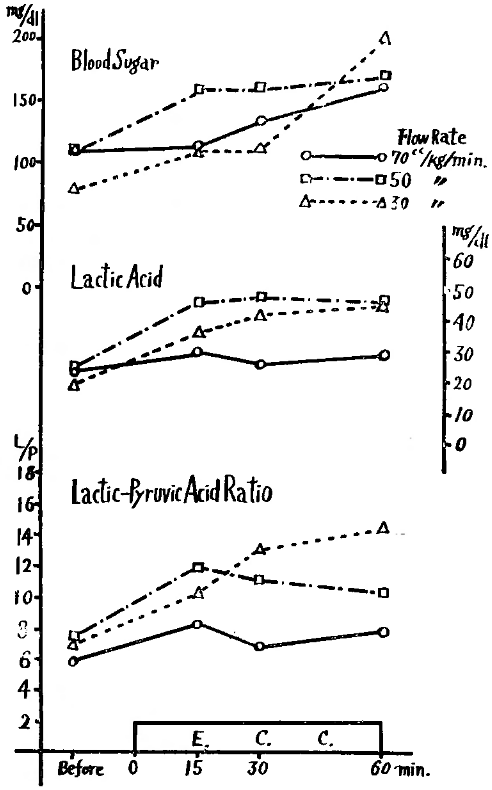


Fig. 11: Changes of blood sugar, lactic acid in the blood, andL/P ratio during total heart lung bypass at mild hypothermia, using pulsatile blood flow with the blood flow rate of 70, 50, and 30cc/kg/min.



C. Discussion

In his animal experiments BIGELOW[1] showed that under conditions of hypothermia, with rectal temperature of the 30° to 25°C, oxgen consumption is reduced from 70% to 50% of normal. However, as described previously, mild hypothermia, especially when induced by surface cooling may cause an increse in blood sugar and lactic acid levels as a result of defence reactions supposedly arisen from the autonomic nervous centers[10)13)27]. Other authors have expressed the opinion that hypothermia induced by extracorporeal circulation may reduce these stress reactions and therefore reduce the tendency to increase blood sugar and lactic acid levels, by inducing a quick hypothermic anesthesia of the responsible nervous centers[12]. The author's experiments showed that, as expected, heart lung bypass causes a greater increase of blood sugar levels when combined with mild hypothermia than under conditions of normothermia. While, after the first 15 minutes of perfusion with hypothermia, the blood sugar level still has a tendency for slight increase, this is not true for the lactic acid. During the period of the second 15 minutes, there was no further increase of these values. After 30 minutes of hypothermic perfusion,

Fig. 12 : Changes of blood sugar, lactic acid, and L/P ratio during total heart lung bypass at mild hypothermia, using non-pulsatile blood flow with the blood flow rate of 70, 50, and 30 cc/kg/min.

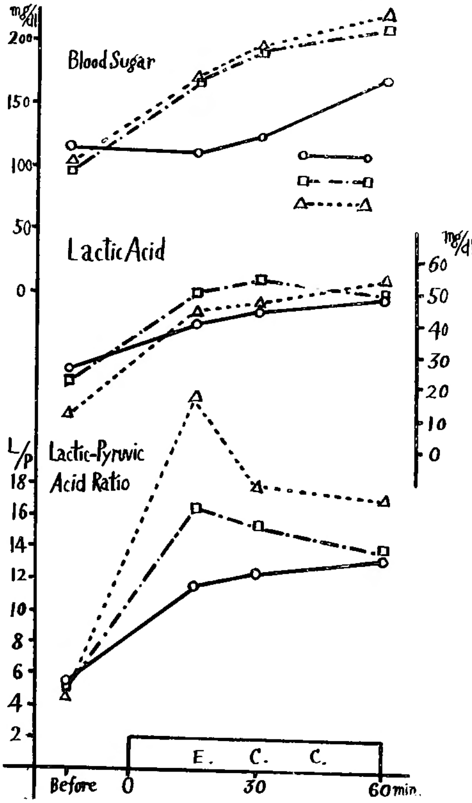


Fig. 13 : Comparisons of lactic acid, pyruvic acid, and L/P ratio between normothermia and mild hypothermia, with a blood flow rate of 50-70 cc/kg/min.

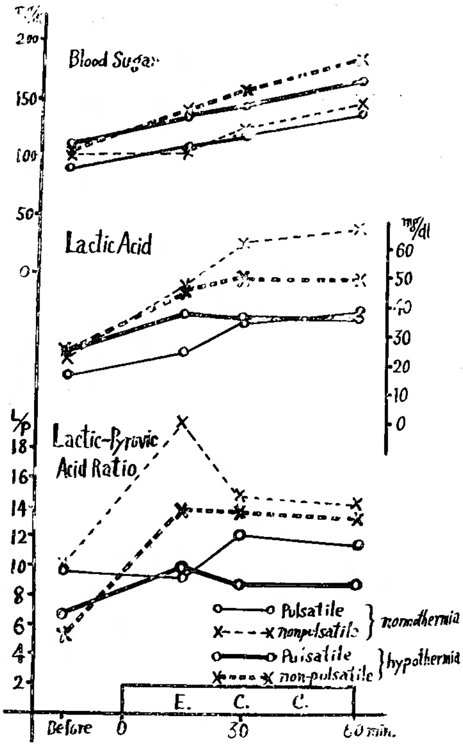


Table 3 Pulsatile Flow Group (Mild Hypothermia)

No.	Flow Rate	Time	Blood Sugar	Lactic Acid	Pyruvic Acid	L/P Ratio
	cc/kg/min.	min.	mg/dl	mg/dl	mg/dl	
53	70	Pre. 15 30 60	109.8 111.5 110.4 152.0	14.5 24.5 18.3 23.2	2.43 2.80 2.98 2.94	5.9 8.7 6.1 7.8
56	50	Pre. 15 30 60	110.5 194.0 170.5 188.6	28.9 42.0 40.8 37.8	3.97 3.70 4.28 3.90	7.3 11.3 9.5 9.6
57	30	Pre. 15 30 60	82.0 110.2 112.9 202.5	18.3 35.0 40.8 44.4	2.62 3.42 3.16 3.08	6.9 10.2 12.9 14.4
63	70	Pre. 15 30 60	110.0 116.0 156.0 173.5	30.5 34.0 32.0 33.3	5.31 4.35 4.24 4.17	5.7 7.8 7.5 7.9
68	50	Pre. 15 30 60	109.5 129.0 147.0 158.0	19.5 49.3 53.3 54.5	2.54 3.90 4.19 4.90	7.6 12.6 12.7 11.1
Average	70	Pre. 15 30 60	109.9 113.7 133.2 162.5	22.5 29.2 25.1 28.2	3.87 3.57 3.61 3.55	5.8 8.2 6.8 7.8
Average	50	Pre. 15 30 60	110.0 161.5 158.7 173.3	24.2 45.6 47.0 46.1	3.25 3.80 4.23 4.40	7.4 11.9 11.1 10.3

the lactic acid values were found lower than under conditions of normothermia during the same period.

The L/P ratio increased more remarkably in the non-pulsatile flow group than in the pulsatile flow group. In both groups, however, the increasing tendency of L/P ratio was much less under hypothermic bypass than normothermic bypass.

In reviewing the above results, it is evident that after heart lung bypass at mild hypothermia of one hour there is a marked increase in lactic acid in the blood and fo the L/P ratio in the non-pulsatile flow group. In the pulsatile flow group under the same conditions, there is no increase in these factors. These facts arouse the suspicion that a non-pulsatile flow somehow disturbs the peripheral circulation and leads to tissue hypoxia even in conjunction with mild hypothermia. These results correspond with the findings of NIIJIMA[13], who pointed out that in mild hypothermia, not below 25°C, the peripheral resistance increases as the reflexes of the autonomic nervous system are still active.

From this point of view, to the authors, it seems advantageous to use pulsatile blood flow during heart lung bypass even under condition of mild hypothermia.

Table 4 Non-pulsatile Flow Group (Mild Hypothermia)

No.	Flow Rate	Time	Blood Sugar	Lactic Acid	Pyruvic Acid	L/P Ratio
	cc/kg/min.	min.	mg/dl	mg/dl	mg/dl	
58	70	Pre.	155.0	26.2	4.80	5.4
		15	124.5	51.3	3.57	14.3
		30	141.5	54.8	3.58	15.3
		60	188.0	62.8	3.57	17.5
59	50	Pre.	84.0	24.8	4.26	5.8
		15	138.0	46.8	3.78	12.3
		30	168.0	48.6	3.58	13.5
		60	226.0	42.5	3.23	13.1
60	30	Pre.	103.0	11.5	2.48	4.6
		15	171.0	44.0	1.87	23.5
		30	194.5	46.0	2.59	17.9
		60	221.0	54.0	3.15	17.1
64	70	Pre.	75.0	24.0	4.21	5.7
		15	97.5	30.2	3.36	8.9
		30	104.5	34.0	3.56	9.5
		60	140.5	35.6	3.94	9.0
70	50	Pre.	110.0	19.5	4.24	4.5
		15	197.0	53.5	2.58	20.7
		30	220.0	60.2	3.35	17.3
		60	196.0	57.5	3.91	14.7
Average		Pre.	115.0	25.1	4.50	5.5
		15	111.0	40.7	3.46	11.6
	70	30	123.0	44.4	3.57	12.4
		60	164.2	49.2	3.75	13.2
Average		Pre.	97.0	22.1	4.25	5.1
		15	167.5	50.1	3.18	16.5
	50	30	194.0	54.4	3.46	15.4
		60	211.0	50.0	3.57	13.9

CONCLUSION

From the viewpoint of carbohydrate metabolism during heart lung bypass under normothermia and mild hypothermia, author investigated the influence of pulsatile blood flow and non-pulsatile blood flow in a series of animal experiments.

(1) Heart lung bypass with normothermia

a. In the non-pulsatile flow group, the blood lactic acid and pyruvic acid levels and the L/P ratio showed a remarkable increase during heart lung bypass even with relative high blood flow rate such as more than 80 cc/kg/min. In the pulsatile flow group, however, almost no changes were observed in lactic aicd and L/P ratio with the same blood flow rate.

b. The extraction rate of lactic acid by the liver was greater in the pulsatile flow group.

c. The increase of blood sugar value was much less in the pulsatile flow group.

d. From these results, it is quite apparent that during heart lung bypass under normothermia the blood stream should be pulsatile and the blood flow rate must be kept more than 80 cc/kg/min.

(2) Heart lung bypass with mild hypothermia

a. The blood lactic acid value and L/P ratio was also better in the pulsatile flow group wtih similar blood flow rate. The results were most satisfactory in the pulsatile flow group with a blood flow rate of 70 cc/kg/min.

b. The blood sugar level with mild hypothermia increased more in both groups than wtih normothermia. However, in the pulsatile flow group the increase was less than in the non-pulsatile flow group.

From the above results, we recommend using pulsatile blood flow during heart lung bypass not only with normothermia, but also even in conjunction with mild hypothermia.

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REFERENCES

1) Allen, J. G. . Extracorporeal Circulation, 2nd Printing, 1960.
2) Anderson, M. N., Buffulo, N. Y., Bo Norberg, Senning, A. . Studies of Liver Function during Extracorporeal Circulation with Low Flow Rate. Surgery, **43**, 397, 1958.
3) Barker, S. and Summerson, W. H. : The Colorimetric Determination of Lactic Acid in Biochemical Material. J. Biol. Chem. **138**, 535-554, 1941.
4) Bigelow, W. G., Lindsay, W. K., Harrison, R. C., Gordon, R. A. and Greenwood, W. F. Oxygen Transport and Utilization in Dogs at Low Body Temperatures. Am. J. Physiol. **160**, 125-137, 1950.
5) Donald, D. E. and E. A. Moffitt, : Study in Extracorporeal Circulation. III. The Relation of Blood Flow and Blood Volume during Extracorporeal Circulation in Man. Surg. Forum, **7**, 264, 1956.
6) Engel, F, L., et al. Biochemical Studies on Shock. I. The Metabolism of Aminoacids and Carbohydrate during Hemorrhagic Shock in the Rat. J. Exper. Med., **77**, 397-410, 1943.
7) Friedmann, T. E. and Haugen, G. E. . Pyruvic Acid. II. The Determination of Keto Acids in Blood and Urine. J. Biol. Chem. **147**, 415-442, 1943.
8) Friedmann, T. E., Haugen, G. E. and Kmieciak, T. C. : Pyruvic Acid (III). The Level of Pyruvic Acid and Lactic Acids, and the Lactic Pyruvic Ratio, in the Blood of Human Subjects. The Effect of Food, Light Muscular Activity, and Anoxia at High Altitude. J. Biol. Chem., **157**, 673, 1945.
9) Gibbon, J. H. . The Lewis A. Conner Memorial Lecture : Maintenance of Cardiorespiratory Function by Extracorporeal Circulation. Circulat., **19**, 646, 1959.
10) Hatano, et al. : Metabolism in Hypothermia. Saishinigaku (Japan), **10**, 350, 1955.
11) Iizima, N. : Lactic Acid and Pyruvic Acid Metabolism in the Field of Surgery, J. Jap. Surg. Society, **50**, 389-389, 1650.
12) Kimoto, S., et al. : Studies of Direct Vision Heart Surgery (Igakushyoin). 433-450, 1958.
13) Knocker, P. : Effects of Experimental Hypothermia on Vital Organ, Lancet, 1955 (II) : 837.
14) Mendelsohn, D., T. N. Mac Krell, M. A. Mac Lacholon, F. S. Cross, and E. B. Kay : Experiences using the Pumpoxygenator for open Cardiac Surgery in Man. Anesthesiology, **18**, 223, 1957.
15) Moffitt, E. A., R. T. Patrick, H. J. C. Swan, and D. E. Donald : A Study of Blood Flow, Venous Blood Oxygen Saturation, Blood Pressure and Peripheral Resistanced During Total Body Perfusion. Anesthesiology, **20**, 18, 1959.
16) Niijima, S. Experimental Study on Hemodynamics During Hypothermic Anesthesia. J. Jap. Surg.

Society, **62**, 102, 1961.
17) Nonoyama, A. Hemodynamic Study on Extracorporeal Circulation with Pulsatile and Non-Pulsatile Blood Flows. Arch. Jap. Chir., **29**, 1381-1406, 1960.
18) Ogata, T., Y. Ida, A. Nonoyama, J. Takeda, and H. Sasaki ; A Comparative Study on the Effectiveness of Pulsatile and Non-Pulsatile Blood Flow in Extracorporeal Circuration. Arch. Jap. Chirur., **29**, 59, 1960.
19) Ogata, T., Y. Ida, A. Nonoyama, and H. Sasaki: Experimental Study on the Extracorporeal Circulation by Use of our Pulsatile Arterial Pump. Lung (Japan), **6**, 381, 1959.
20) Russel, J. A., et al. : Biochemical Studies on Shock. II. The Role of the Peripheral Tissues on the Metabolism of Protein and Carbohydrate during Hemorrhagic Shock in the Rat. J. Exper. Med., **79**, 1-7, 1944.
21) Saegusa, M. et al. . Studies on Hepatic Circulation, Liver Function, Renal Circulation, and its Function During Extracorporeal Circulation. Jap. J. Thor. Surg., **12**, 993, 1959.
22) Salisbury, P. F. : Extracorporeal Circulation as an Aid to Cardiac Surgery (Handbuch der Thoraxchirurgie. p. 694, Springer-Verlag, Berlin, Goettingen Heidelberg, 1958.
23) Samuel Soskin, and Rachmiel Levine Carbohydrate Metabolism. 2nd Edition, the University of Chicago Press, 1952.
24) Shibusawa, K, : Studies on Shock J. Jap. Surg. Society, **50**, 224-243, 1949.
25) Somogyi, M. . Notes on Sugar Determination. J. Biol. Chem. **195**, 19, 1952.
26) Starr, A. : Oxygen Consumption During Cardiopulmonary Bypass. J. Thorac. Surg., **38**, 46, 1959.
27) Takahashi, Y. : The Blood Level of Carbohydrate Intermediates and Inorganic Phosphorus under the Influence of Direct Vision Heart Surgery Usiing Extacorrporeal Circulation. Med. J. Osaka Univ. (Japan), **11**, 263-270, 1959.
28) Takeda, J. . Experimental Study on Peripheral Circulation during Extracorporeal Circulation, with a Special Reference to a Comparison of pulsatile Flow with Non-Pulsatile Flow. Arch. Jap. Chir., **29**, 1407, 1960.
29) Waud, R. A. The Use of the Artificial Heart-Lung in Pharmacology. Trans. Amer. Soc. Artif. Int. Org., **1**, 87, 1955.

UNTERSUCHUNGSERGEBNISSE DES KOHLENHYDRATSTOFFWECHSELS BEIM ANWENDEN DES EXTRACORPORELLEN KREISLAUFES, BESONDERS IN BEZUG AUF DEM VERGLEICH DER PULSATORISCHEN BLUTSTROMS MIT DEM UNPULSATORISCHEN BLUTSTROM

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Es ist noch nicht entschieden, was für einen Einfluß beim Anwenden des extracorporellen Kreislaufes der pulsatorische und unpulsatorische Blutstrom je auf den peripheren Kreislauf übt.

Um dies zu erforschen, haben wir das Experiment über den extracorporellen Kreislauf gemacht mit der Normothermie und der Hypothermie unter dem pulsatorischen und unpulsatorischen Blutstrom, und die Veränderungen des Kohlenhydratstoffwechsels dabei betrachtet.

Das Ergebnis ist wie folgt:

(1) Die Veränderung der Milchsäure und der Benztraubensäure im Blute beim Anwenden des extracorporellen Kreislaufes mit Normothermie.

a. In der Unpulsgruppe nahmen die Milchsäure, die Benztraubensäure in Blut und der M/B Quotient (Milchsäure/ Benztraubensäure) zu, sogar bei den Fällen, deren Stromvolum mehr als 80 cc/kg/Min. war. Dagegen in der Pulsgruppe waren diese Veränderungen nicht zu bemerken.

b. Die Fähigkeit des Lebers Milchäure zu ausscheiden war in der Pulsgruppe stärker als in der Unpulsgruppe.

c. Auch die Zunahme des Blutzuckers war in der Pulsgruppe weniger als in der Unpulsgruppe.

Hieraus ist zu schließen, daß beim Anwenden des extracorporellen Kreislaufes mit Normothermie ist der pulsatorische Blutstrom vonmehr als 80 cc/kg/min. erforderlich.

(2) Die Veränderung der Milchsäure und der Benztraubensäure im Blut beim Anwenden des extracorporellen Kreislaufes mit leichtgraden Hypothermie.

a. Die Zunahme der Milchsäure im Blut und des M/B Quotienten war in der Pulsgruppe weniger als in der Unpulsgruppe. Besonders in den Fällen mit Blutstrom 70cc/kg /min. war die Zunahme der Milchsäure im Blut und des M/B Quotienten kaum bemerkbar.

b. Beim extracorporellen Kreislauf mit der leichtgraden Hypothermie nahme der Blutzucker in beiden Gruppen zu als mit der Normothermie.

Daraus kann man schließen, daß beim Anwenden des extracorporellen Kreislaufes sowohl mit der Normothermie als auch mit der leichtgraden Hypothermie ist der pulsatorische Blutstrom durchaus notwendig.

和　文　抄　録

完全体外循環に関する実験的研究

特に完全体外循環の施行に際して脈動の有無が糖質代謝に及ぼす影響について

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井　田　喜　三

人工心肺装置を使用して完全体外循環を行うに際して，脈動流並に無脈動流が末梢循環にどのような影響を及ぼすかという点についてはなお充分な究明がなされていない．そこで，著者はこの点を究明する目的で，常温下並に軽度低体温下に，脈動流及び無脈動流を使用して完全体外循環を行い，その際の血中糖質代謝の推移を観察して，次のような結論に到達した．

(1) 常温に於て完全体外循環を行つた際の血中乳酸，焦性葡萄酸及び血糖値の推移

a. 無脈動流群では80cc/kg/min. 以上の流量で体外循環を行つても，なお血中乳酸値，焦性葡萄酸値及びL/P比は著しい増加を示した．併し脈動流群では同一流量で体外循環を行う限り，血中乳酸値やL/P比の増大は殆ど認められなかつた．

b. 肝臓に於ける乳酸処理能についてみても，脈動流群の方が無脈動流群よりも，それは良好に保たれた．

c. 血糖値の増加も脈動流群の方が小であつた．

以上の成績から，常温下に於て体外循環を行う際には，80cc/kg/min. 以上の脈動流を使用した方がよろしいとの結論に到達した．

(2) 軽度低体温下に完全体外循環を行つた際の血中乳酸，焦性葡萄酸及び血糖値の推移

a. 血中乳酸値及びL/P比は同一流量では脈動流群の方がその増加の程度が軽微であつた．殊に70cc/kg/min. の脈動流を使用した場合には乳酸値及び L/P 比とも殆どその増加が認められなかつた．

b. 軽度低体温法を併用すると，血糖値は両群とも常温下に於て体外循環を行つた際よりも一層顕著な増加を示した．併し脈動流群の方が無脈動流群よりもその増加の程度が小であつた．

以上の成績から，常温下に於ては勿論，軽度低体温下に体外循環を行うに当つても，無脈動流では多少共末梢循環障は害され，ひいては組織の Hypoxia を招く怖れのあることが考えられ，従つて著者は体外循環を行うに際しては常温下に於ては勿論，軽度低体温下に於ても脈動流を以て体外循環を行うことが必要な処置であると考えるに至つた．